



EVOLUZIONE DELL'ALGORITMO TERAPEUTICO DEL PAZIENTE CON LAM

Esperienza di pratica clinica nel paziente Fit a rischio favorevole

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Caso clinico 1

Uomo, 55 aa

Gennaio 2020

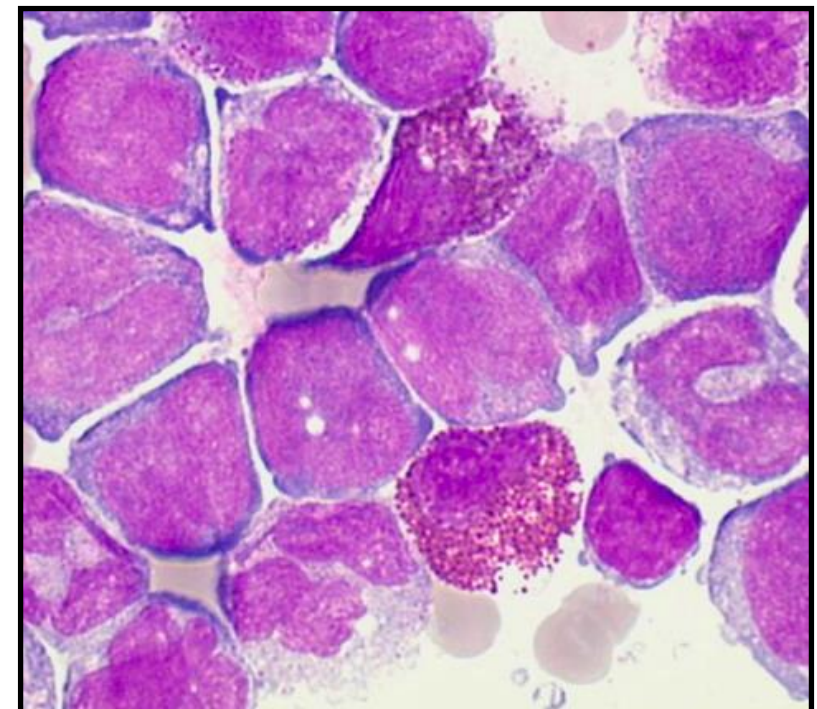
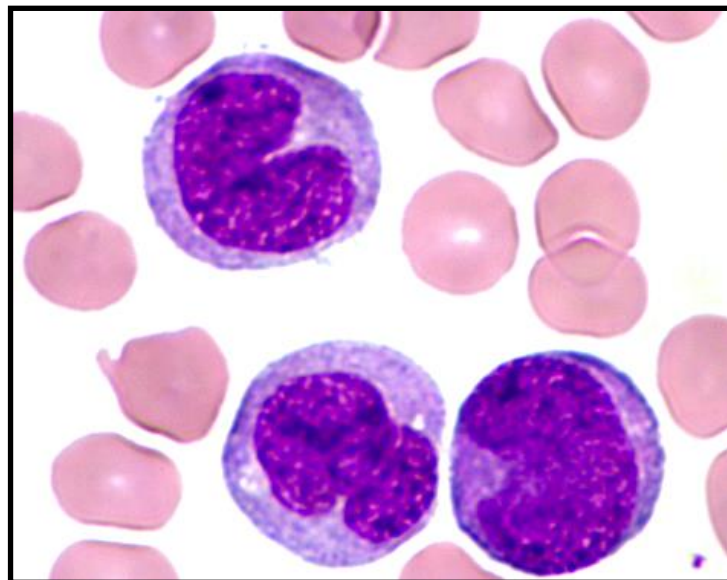
09.01.2020: Accesso in P.S per febbre persistente da giorni, leucocitosi ed ascite

(GB 35.000, Hb 12,1 Plt 131.000)

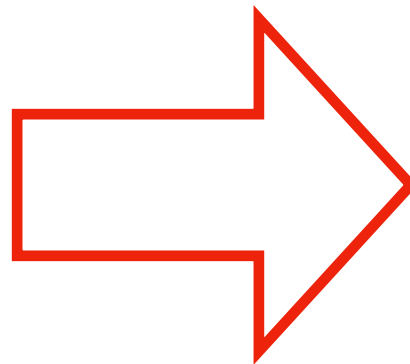
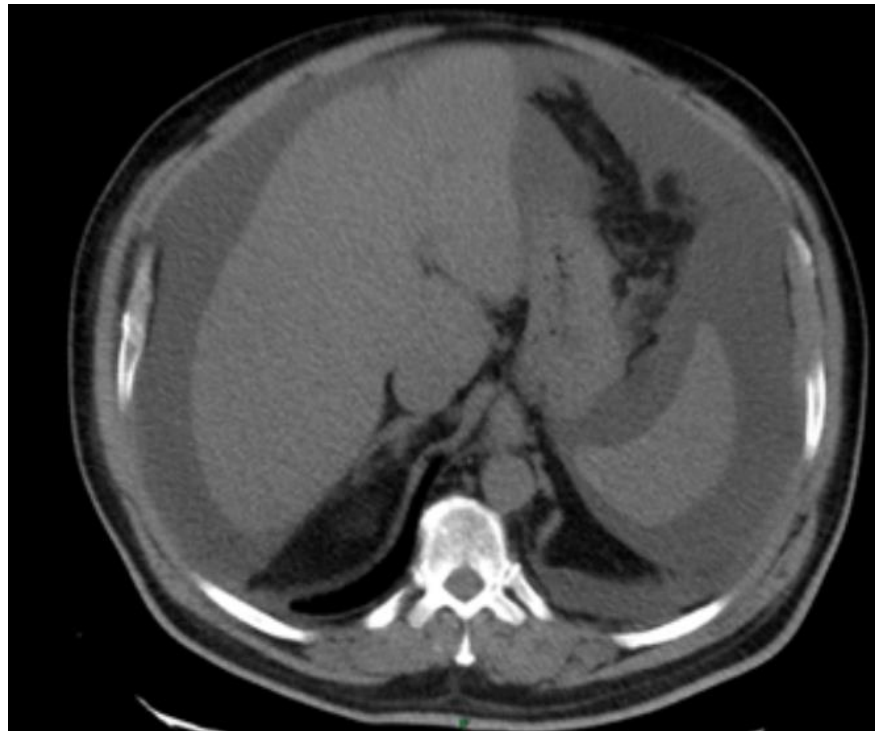
Diagnosi di “Acute leukemia with NPM mutation” (WHO 2016), CD33+ (>75%)

Rischio citogenetico-molecolare (ELN2017): low

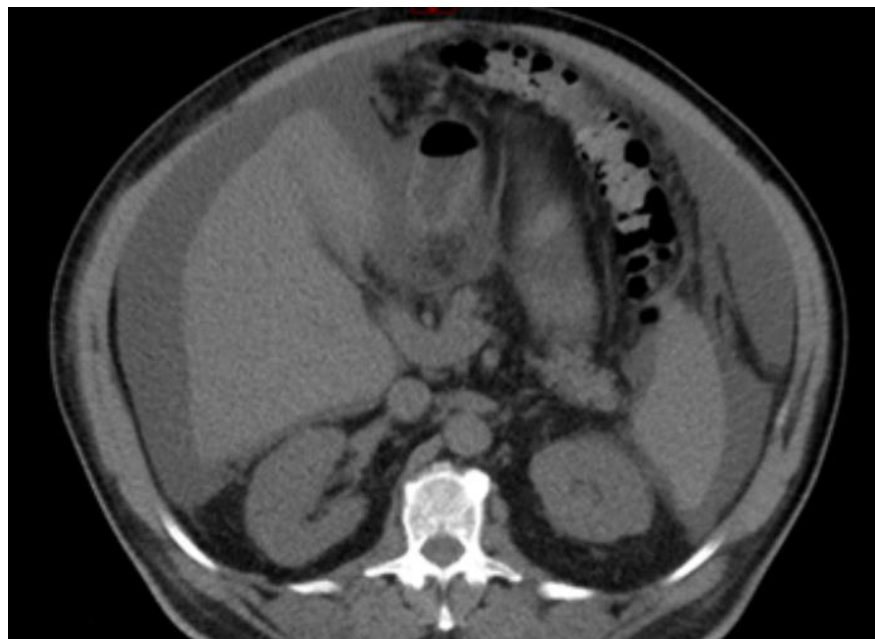
46, XY; NPM1 mut (mut A), FLT3ITD/D835 neg, p53wt



TC ADDOME DEL 10/01/2021 (eseguita per addome ascitico)



“Abbondante versamento ascitico sopra e sotto-mesocolico con aspetto disomogeneo del grasso peritoneale [...] i reperti depongono per carcinosi peritoneale”



**SECONDA NEOPLASIA??
LOCALIZZAZIONE DI AML??**

“Acute Luekemia with NPM1 mut” (WHO 2016)

rischio citogenetico -
molecolare: low
localizzazione extramidollare
(peritoneale)

IMMUNOFENOTIPO:		
Gate	Antigene	%
TNC	CD45 ^{BRIGHT} +CD33+CD117-/+CD36+CD64+CD56+	26

IMMUNOFENOTIPO SU LIQUIDO ASCITICO

POS= antigene espresso (≥75%)	NEG= antigene non espresso (≤3%)	+/- = antigene parzialmente espresso (≥20%)	-/+ = antigene parzialmente espresso (≤20%)
ANALISI CITOMETRICA: Individuata una popolazione cellulare, con profilo immunofenotipico e caratteristiche fisiche compatibili con quelle dei blasti individuati nell'analisi del sangue periferico, pari al 26% della cellularita' totale riscontrata nel campione di liquido ascitico.			
CONCLUSIONI: Presente localizzazione ascitica di processo mieloproliferativo.			

Materiale inviato Liquido ascitico	ES. CITOLOGICO LIQUIDO ASCITICO
Notizie Cliniche Leucemia acuta mieloide M5a	
COMUNICAZIONE DI ESAME CITOLOGICO	
Microscopica Materiale ematico comprendente una popolazione cellulare di elementi ad abito blastico di media taglia con citoplasma eosinofilo e con nucleo rotondo-ovalare a volte convoluto. Tali elementi mostrano immunoreattività per CD68PGM1, MPO, CD15, e immunonegatività per CD56, CD2 (+ in un modesto numero di linfociti T), CD117, CKAE1/AE3, TdT, CD34, CKAE1/AE3. La reazione con il marcatore NPM mostra una regolare espressione nucleare della nucleofosmina e talora citoplasmatico di dubbio significato.	
Diagnosi Versamento leucemico riferibile a leucemia acuta a differenziazione mielomonocitica.	

**17.01.2020: Inizia chemioterapia di induzione
con “3+7”+GO**

24.02.2020: Valutazione della risposta al recupero
ematologico

GB 2250 (N 570), Hb 10,5, Plt 53.000

Agoaspirato midollare: blasti 8%, SD delle
localizzazioni peritoneali e dell'ascite

15.03.2020: Inizia chemioterapia di seconda linea secondo schema MEC (mitoxantrone 6mq/mq gg1—5; Etoposide 100mg/mq gg 1—5; AraC 1gr/mq gg1—5)

16.04.2020: Valutazione della risposta al recupero ematologico
CR morfologica ed immunofenotipica (MRD 0.01% su 1.000.000 di eventi) con regressione delle lesioni peritoneali e dell'ascite

TC addome del 18.04: “ riduzione di più del 75% delle lesioni omentali e mesenteriche, assente ascite”

Dopo un ciclo di consolidamento il paziente viene avviato ad **AlloH SCT**
(related donor, fratello HLA compatibile)

NO VOD, aGVHD cutanea grado II (responsiva a terapia steroidea)

28.10.2026 (+ 6 anni da TMO): vivo, in CR, NO cGVHD

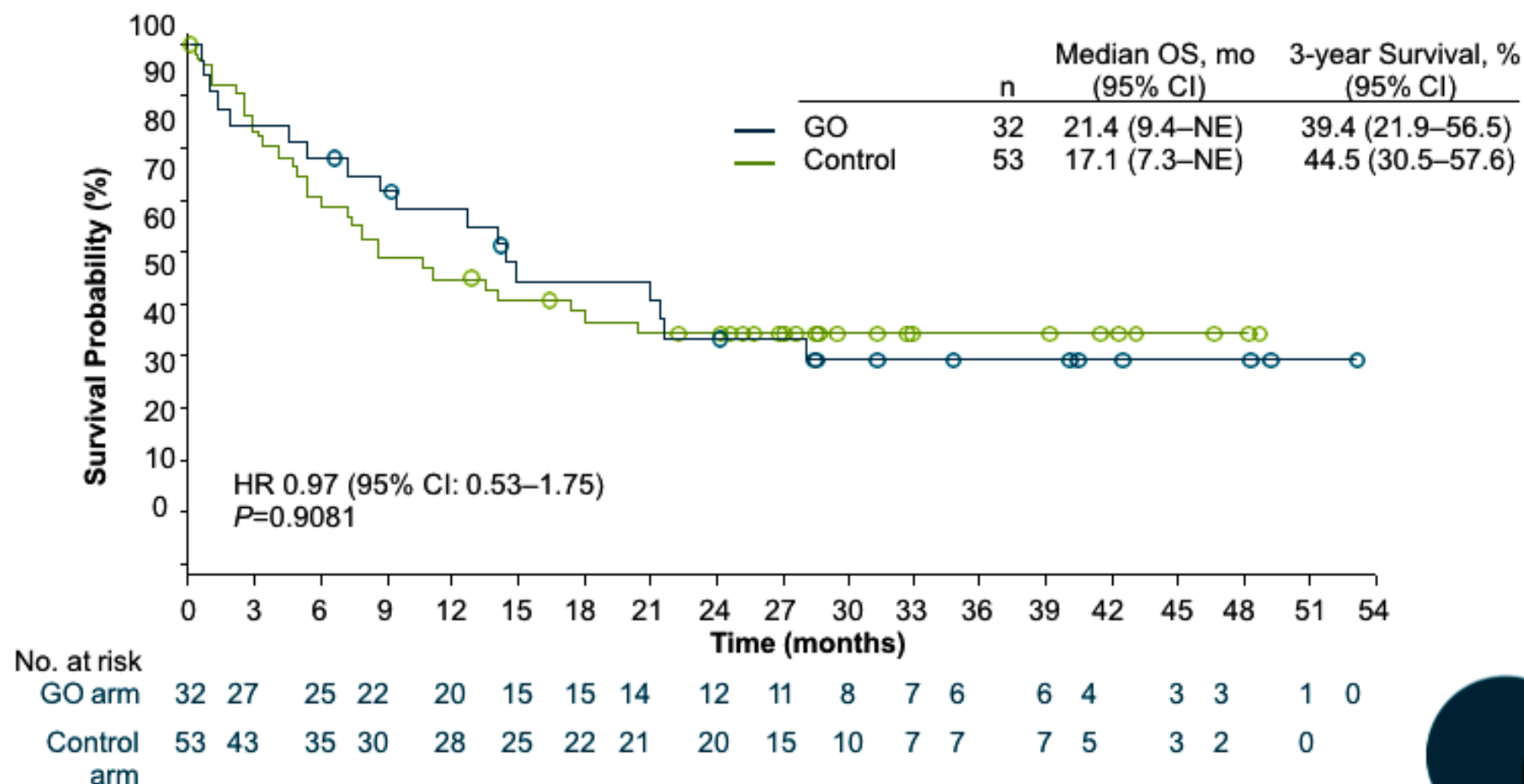
Outcomes Following Hematopoietic Stem Cell Transplantation in Patients Treated With Chemotherapy With or Without Gemtuzumab Ozogamicin for Acute Myeloid Leukemia

Cécile Pautas¹ • Emmanuel Raffoux² • Juliette Lambert³ • Olivier Legrand⁴ • Sylvain Chantepie⁵ • Lauris Gastaud⁶ • Jean-Pierre Marolleau⁷ • Xavier Thomas⁸ • Pascal Turlure⁹ • Rebecca J. Benner¹⁰ • Erik Vandendries¹¹ • Karim Gogat¹² • Hervé Dombret² • Sylvie Castaigne¹³

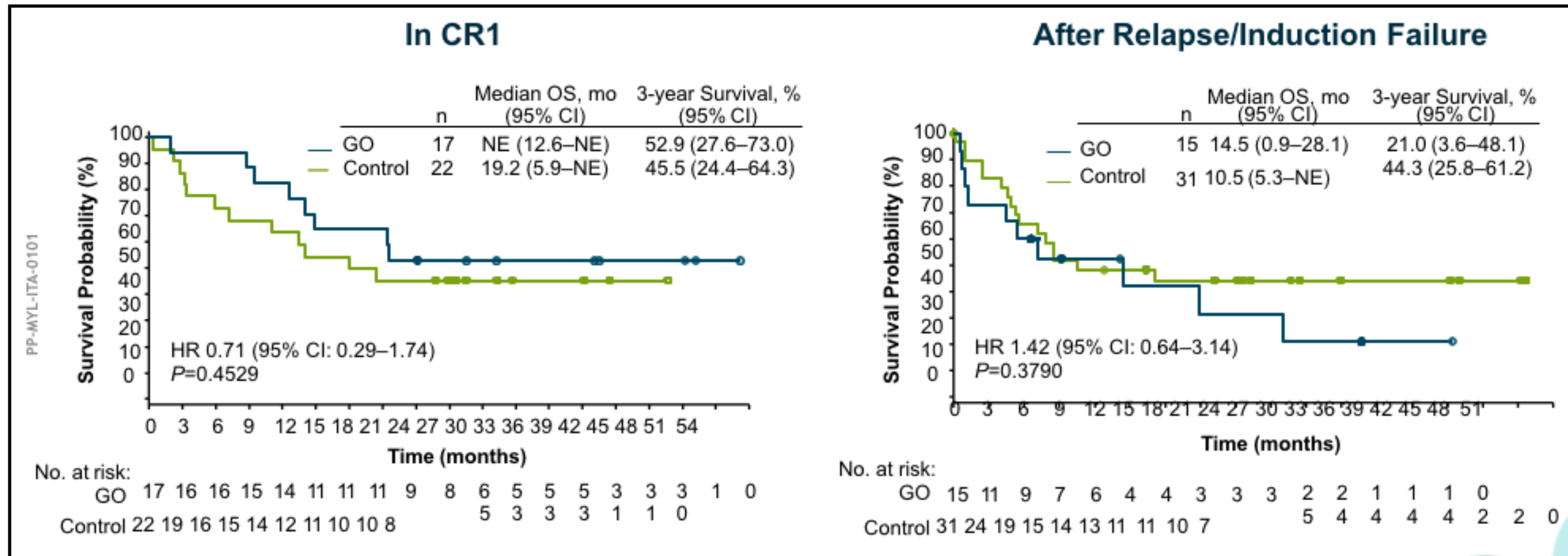
- The objectives of this retrospective analysis were to describe transplant characteristics and to examine survival and VOD outcomes in patients who received HSCT in the ALFA-0701 trial

85 patients (GO arm: n=32; control arm: n=53) received HSCT during the study

- An interval of 2 months between last dose of GO and transplant was recommended



Post-Transplant Survival in Patients Receiving Transplant in CR1 or After Relapse/Induction Failure*



* Relative to EFS event; patients who received HSCT after relapse or induction failure could have achieved subsequent CR prior to HSCT.

CI=confidence interval; CR=complete remission; EFS=event-free survival; GO=gemtuzumab ozogamicin; HR=hazard ratio;

HSCT=hematopoietic stem cell transplantation; NE=not estimable;

OS=overall survival

Pautas C et al Bone Marrow Transplant. 2021 Feb 9. doi: 10.1038/s41409-020-01207-4.

Survival did not differ significantly between the treatment arms in patients that received HSCT

- Patients from ALFA-0701 who received a HSCT were retrospectively analysed (GO arm, n=32; control arm, n=53*)
- Median post-transplant survival was 21.4 months with GO versus 17.1 months in the control arm (HR: 0.97; P=0.9081)
- VOD was reported in five patients in total; three cases occurred post-transplant

Treatment arm	Grade	Outcome	Timing
Control†	3	Recovered	Post-transplant
Control†	4	Recovered	Pre-transplant
GO	4	Died before VOD resolved	Post-transplant‡
GO§	3	Recovered	Pre-transplant
	3	Recovered	Post second transplant
GO	2	Recovered	Pre-transplant

GO can be used as part of induction and consolidation chemotherapy prior to HSCT

Adapted from Pautas C et al. Bone Marrow Transplant. 2021 Feb 9. doi: 10.1038/s41409-020-01207-4.

*All patients received allogeneic HSCT, apart from one patient in the control arm who received autologous HSCT; †Patient received gemtuzumab ozogamicin as follow-up therapy; ‡Patient developed VOD during conditioning regimen for HSCT;

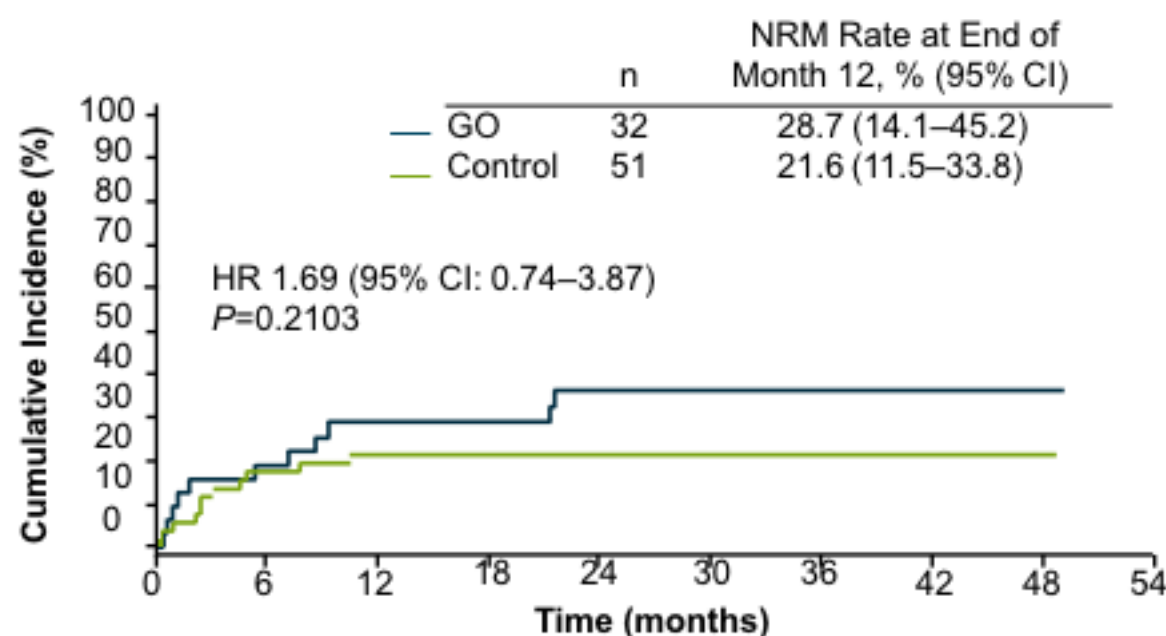
§Patient experienced two events of VOD; gemtuzumab ozogamicin was discontinued after the first event

GO, gemtuzumab ozogamicin; HSCT, haematopoietic stem cell transplantation; VOD, veno-occlusive disease

Pautas C et al. Bone Marrow Transplant. 2021 Feb 9. doi: 10.1038/s41409-020-01207-4.

GO-ALFA 07-01: Non-relapse Mortality and Cumulative Incidence of Relapse After Transplant

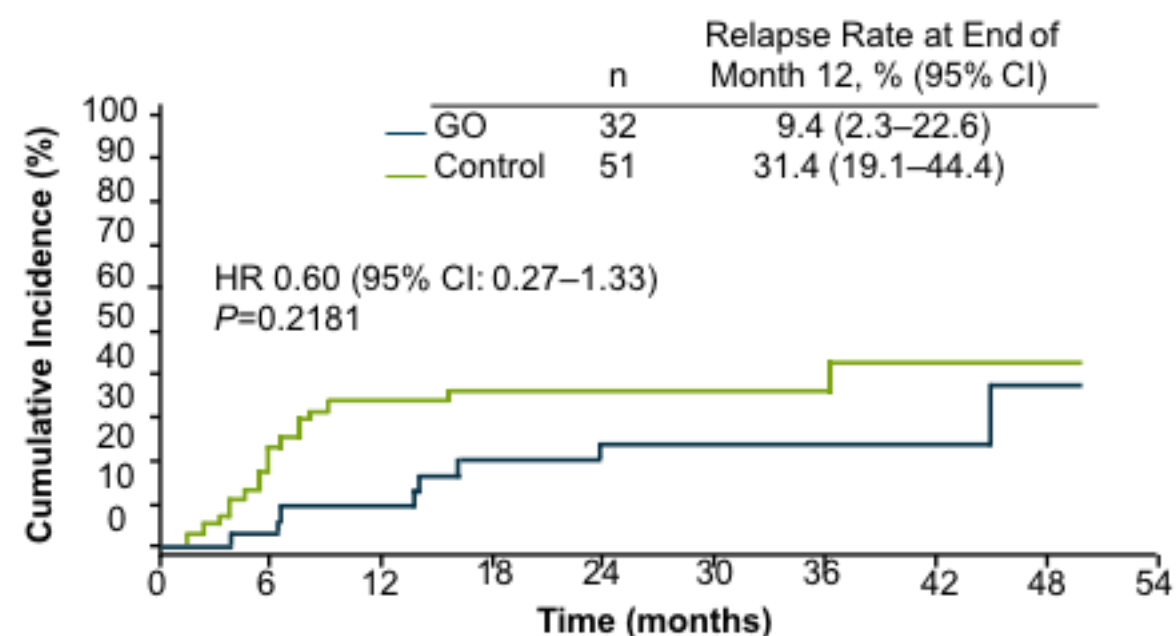
Nonrelapse Mortality*



No. at risk:

GO	32	25	25	14	14	8	8	4	4	0
Control	51	31	31	21	21	10	10	4	4	0

Cumulative Incidence of Relapse†



No. at risk:

GO	32	25	25	14	14	8	8	4	4	0
Control	51	31	31	21	21	10	10	4	4	0

* Competing event is relapse after HSCT or any death post HSCT related to relapse, whichever occurs first. † Competing event is death due to causes unrelated to relapse.

CI=confidence interval; GO=gemtuzumab ozogamicin; HR=hazard ratio; HSCT=hematopoietic stem cell transplantation; NRM=nonrelapse mortality

Pautas C et al Bone Marrow Transplant. 2021 Feb 9. doi: 10.1038/s41409-020-01207-4.

GO and extramedullary disease

Case Study | Published: August 2007

Gemtuzumab therapy for isolated extramedullary AML relapse following allogeneic stem-cell transplant

[Taofeek Owonikoko](#), [Mounzer Agha](#), [Ronald Balassanian](#), [Ryan Smith](#) & [Anastasios Raptis](#) 

[Nature Clinical Practice Oncology](#) 4, 491–495 (2007) | [Cite this article](#)

ONLINE ARTICLES: CLINICAL AND LABORATORY OBSERVATIONS

Clinical and Radiographic Response of Extramedullary Leukemia in Patients Treated With Gemtuzumab Ozogamicin

McNeil, Michael J. MD^{*}; Parisi, Marguerite T. MD, MS^{*,†}; Hijiya, Nobuko MD^{‡,§}; Meshinchi, Soheil MD, PhD[‡]; Cooper, Todd DO^{*,‡}; Tarlock, Katherine MD^{*,‡}

[Author Information](#) 

Gemtuzumab ozogamicin therapy for isolated extramedullary AML relapse after allogeneic hematopoietic stem-cell transplantation

[Toshihiko Ando](#) ¹, [Noriyuki Mitani](#), [Kimie Matsunaga](#), [Tatsuki Nakazora](#), [Toshikazu Gondo](#), [Toshiaki Yujiri](#), [Yukio Tanizawa](#)

The 65th ASH Annual Meeting Abstracts

Outcomes of Extramedullary Acute Myeloid Leukemia with Gemtuzumab Ozogamicin: Real-World Experience

Riya Patel, MBBS¹, Khalid Shalaby, MBBCh¹, Charles Roche, MD², Hassan Awada, MD², Elizabeth A. Griffiths, MD³, James E Thompson, MD³, Steven Green, MD¹, Pamela Jeannette Sung, MDPhD³, Eunice S. Wang, MD⁴, Amanda C. Przepolewski, DO⁴

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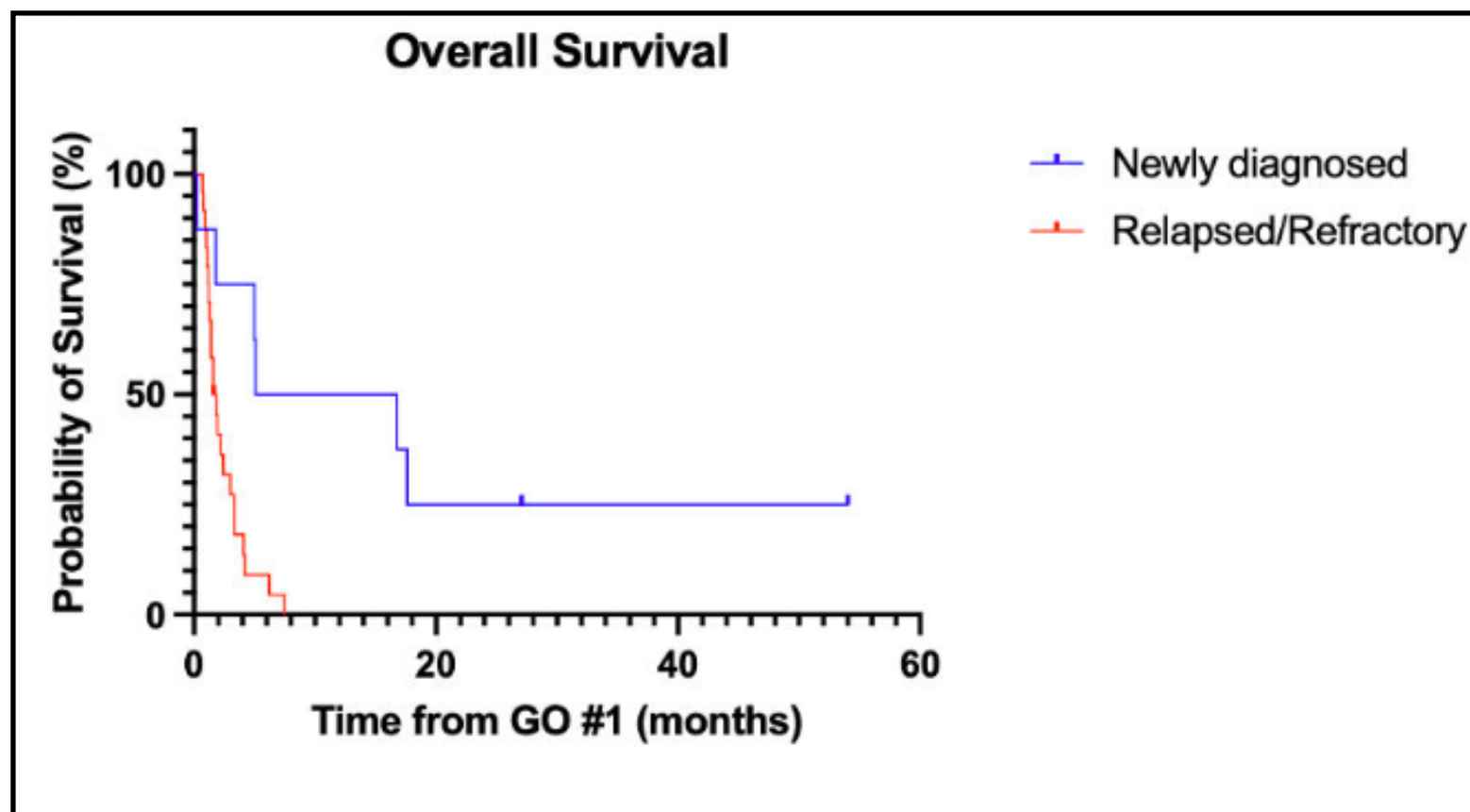
⁴ Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

32 pz with EM AML : 8 (25% ND), 22 R/R AML

EM-AML were: skin (25%), lymph nodes (25%), soft tissues (25%), solid organs (25%), and visceral body cavity fluids (12.5%)

ELN 2022 risk group: 17 patients were adverse, 8 with intermediate, and 3 with favorable risk

GO-based treatment regimens		
GO monotherapy	1 (12.5%)	0
Cytarabine, daunorubicin	3 (37.5%)	10 (41.67%)
Cytarabine, daunorubicin, etoposide	0	3 (12.5%)
Decitabine, venetoclax	0	2 (8.33%)
Decitabine	2 (25%)	1 (4.2%)
Outcomes by RECIST criteria		
Complete remission	4 (50%)	2 (4%)
Partial response	1 (12.5%)	12 (50%)
Refractory/progression/persistent disease	2 (25%)	12 (50%)
Stable disease	0 (0%)	8 (33%)
NA	1 (12.5%)	8 (33%)
Bone marrow transplant (AlloBMT)		
BMT prior to GO	0	12 (50%)
BMT after GO	3 (37.5%)	0
Relapse after AlloBMT	1 (12.5%)	12 (50%)
Median Overall Survival (months)	10.91 (0.2- 27.1)	1.58 (0.7 – 7.5)
30-day mortality (%)	1 (12.5%)	2 (8.3%)
60-day mortality (%)	2 (25%)	12 (50%)



Median OS: 10.91 months for ND EM AML and 1.58 m for R/R EM-AML

(3 of 8 newly diagnosed EM-AML underwent allogeneic bone marrow transplant after GO based induction, followed by relapsed EM AML in 1 patient)

Based on RECIST criteria, 7 of 11 (63.63%) pts achieved a response including 1 Complete Response (disappearance of all target lesions), 6 Partial Response (at least a 30% decrease in the sum of target lesions), and 2 Stable Disease (neither sufficient shrinkage nor increase).

The 30-day mortality for ND and R/R were 12.5% and 8.33%, respectively. The 60-day mortality for ND and R/R were 25% and 50%, respectively.

Caso clinico 2

Uomo, 60 aa



ANAMNESI PATOLOGICA REMOTA

Ipertensione arteriosa in trattamento, in buon compenso

Ipercolesterolemia in trattamento

Ipertrofia prostatica benigna

**20.09.2024: accesso in PS per anemia,
piastrinopenia e leucocitosi**

(GB 35.000, Hb 9,1 Plt 58.000)

Esame morfologico da PB: circa 30% di blasti mieloidi

Agoaspirato midollare: Infiltrazione diffusa da blasti mieloidi (circa 80%)

Citofluorimetria: CD45 dim, CD34 +, CD117+, HLA-DR+, CD13+,
CD33+bright, CD15+, CD64 ±, CD14 ±, MPO+, CD11b ±, CD7 ±, CD56 ±

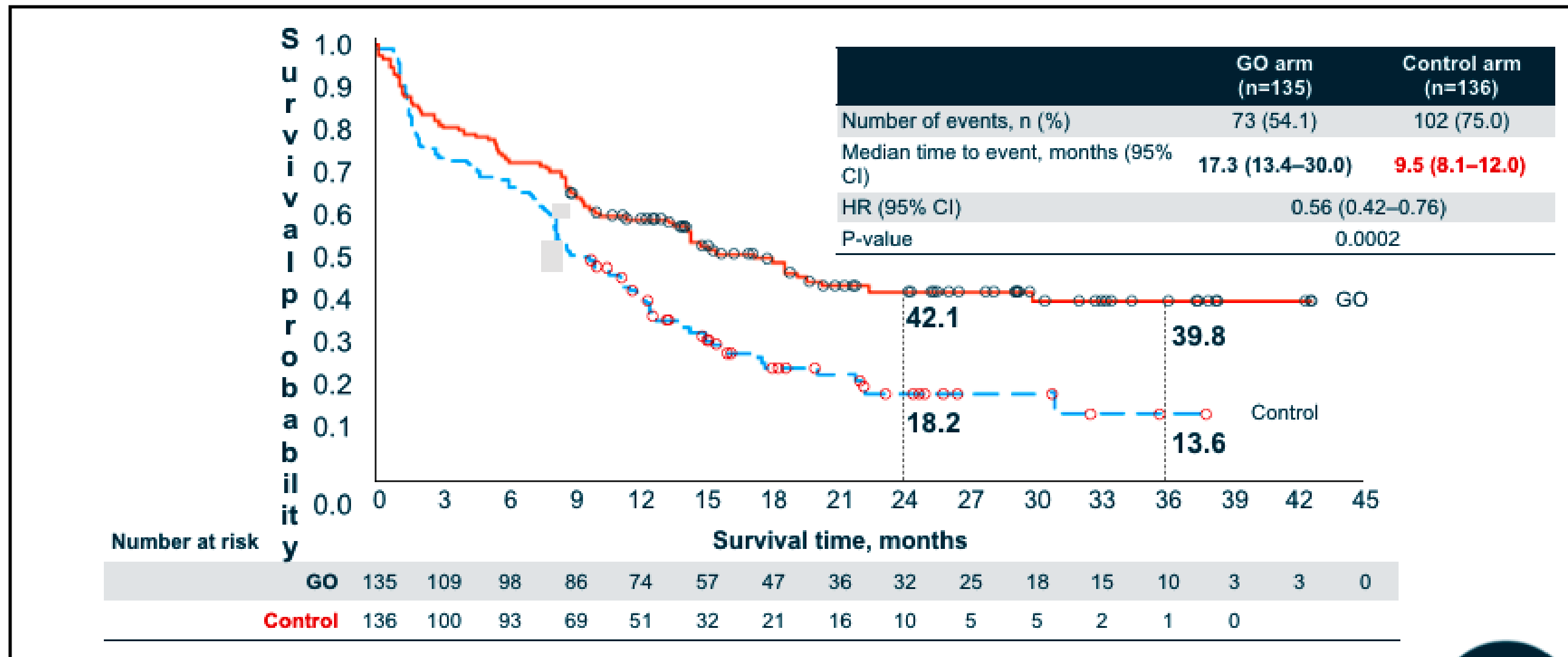
Analisi citogenetica: 46, XY [20]

Analisi molecolare: NPM1 mut (mut tipo A), FLT3 [ITD/TKD] wt, RUNX1 wt,
CEBPA wt, TP53wt, IDH1-2 wt

**Diagnosi di “Acute leukemia with NPM mutation” (WHO 2022),
CD33+ (>75%)**

Rischio citogenetico-molecolare (ELN2022): low

ALFA-0701: Event-free survival (primary endpoint)



Adapted from Lambert et al. 2019

Modified intention-to-treat population; Data cut-off date: 1 August 2011

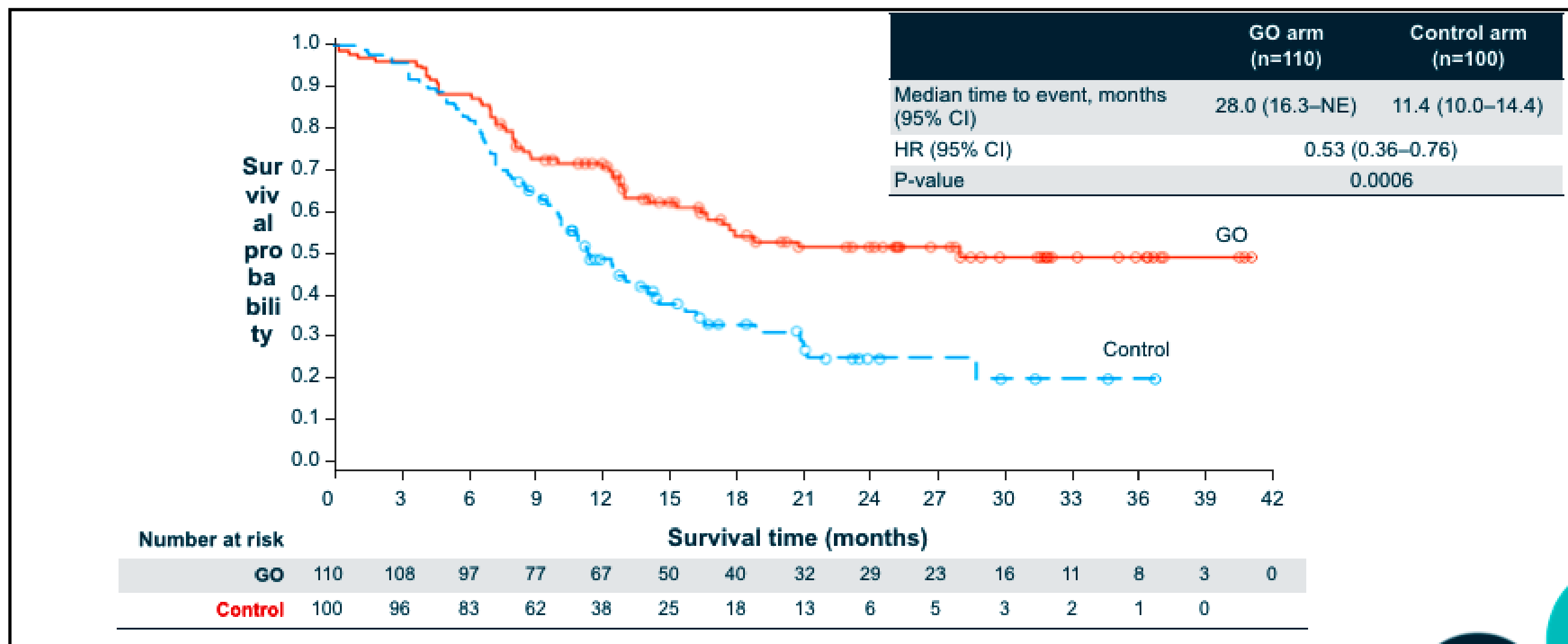
CI, confidence interval; GO, gemtuzumab ozogamicin; HR, hazard ratio

Lambert J et al. Haematologica 2019;104:113–119

ALFA-0701: Event-free survival at 2 and 3 years

	GO arm (n=135)	Control arm (n=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Induction failure	17 (12.6)	29 (21.3)
Relapse	44 (32.6)	58 (42.6)
Death	12 (8.9)	15 (11.0)
Number of censored subjects, n (%)		
Event-free at reference date	62 (45.9)	34 (25.0)
Long-term analysis		
Probability of being event-free at 2 years (95% CI)	42.1 (32.9–51.0)	18.2 (11.1–26.7)
Probability of being event-free at 3 years (95% CI)	39.8 (30.2–49.3)	13.6 (5.8–24.8)

ALFA-0701: Relapse-free survival



Adapted from Lambert *et al.* 2019 (Suppl.)

Per investigator. mITT population; circles indicate censored observations

CI, confidence interval; GO, gemtuzumab ozogamicin; HR, hazard ratio; mITT, modified intention-to-treat

Lambert J *et al.* *Haematologica* 2019;104:113–119 (Suppl.)

**02.10.2024: Chemioterapia di induzione: DNR 60 mg/mq day1-3,
ARA-C 100 mg/mq day 1-7, GO 3 mg/mq day 1,4,7.**

Profilassi: posaconazolo

Complicanze: mucosite G1/2, FUO

Assenza di tossicità epatica significativa (transaminite G1 della durata di 5 giorni)

29 ottobre 2024 (g+27): CR morfologica e citofluorimetrica

Neutrofili > 1000/mmc al giorno 28

Piastrine > 50.000/mmc al giorno 35

Novembre 2024-gennaio 2025: Chemioterapia di consolidamento (due cicli) con DNR, ARA-C, GO

Assenza di eventi avversi extra-ematologici in entrambi i cicli

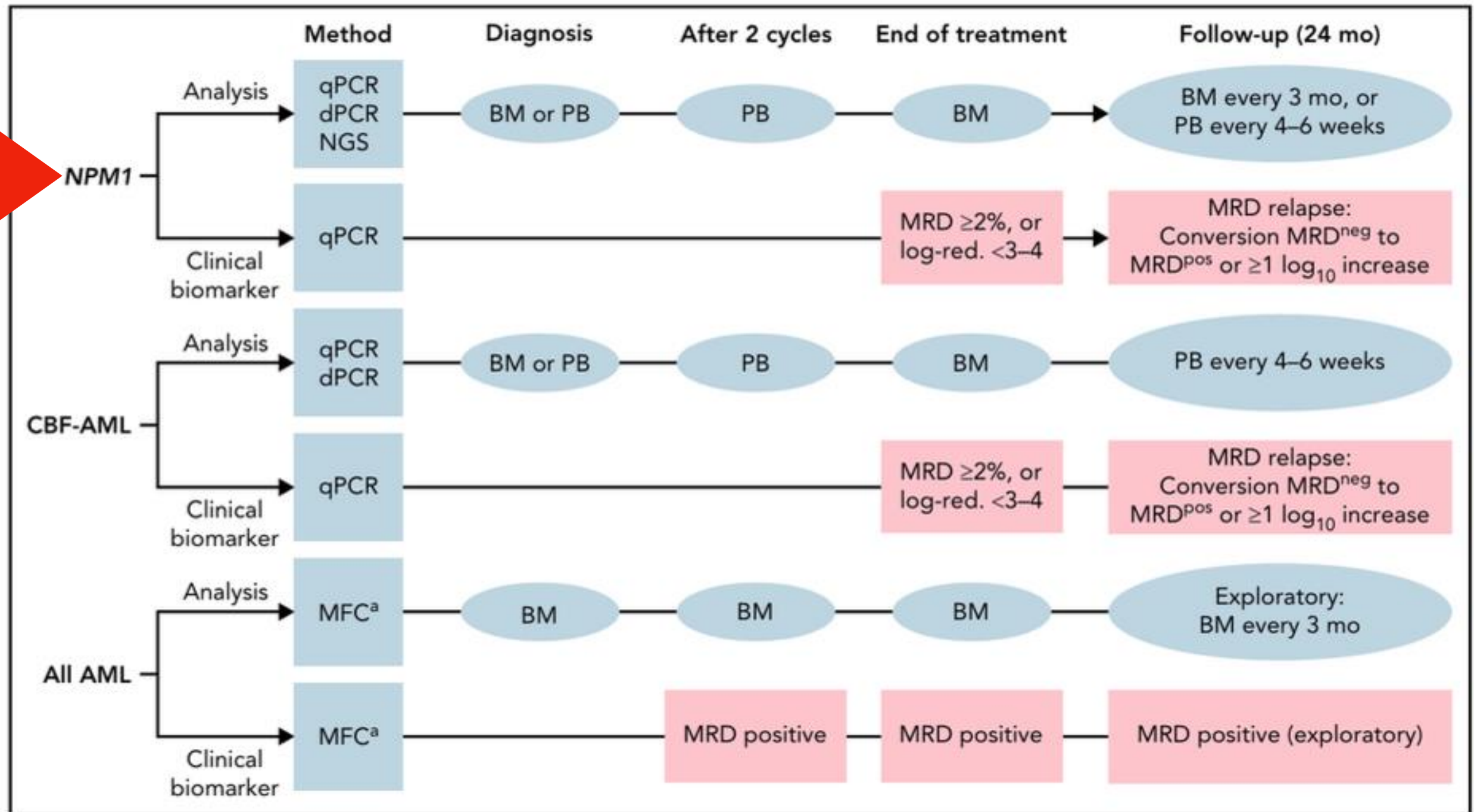
Piastrinopenia con recupero di conta $> 100.000/\text{mmc}$ al giorno 41 durante il secondo ciclo e dopo 5 mesi dalla fine del terzo ciclo

Dicembre 2024 e Febbraio 2025: Valutazione midollare, post C1 e EOT: CR, MRD neg

Prosecuzione delle valutazioni midollari ogni tre mesi

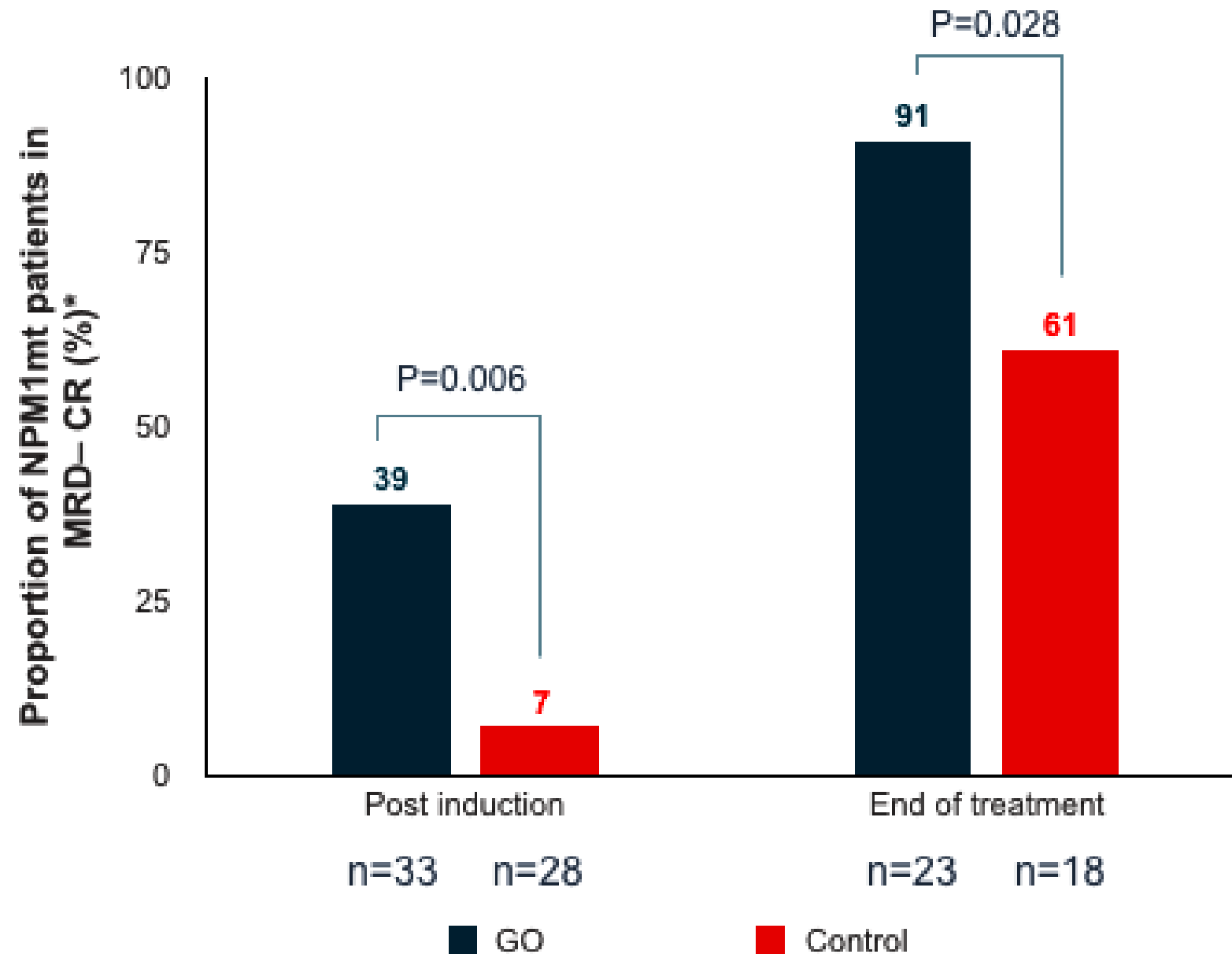
Aprile 2026: CMR a 14 mesi dalla fine del trattamento (MRD 0.012)

Algorithm of MRD assessment and time points at which MRD is considered a Clinically relevant biomarker



Effect of GO Treatment on MRD

ALFA-0701: Minimal residual disease negativity



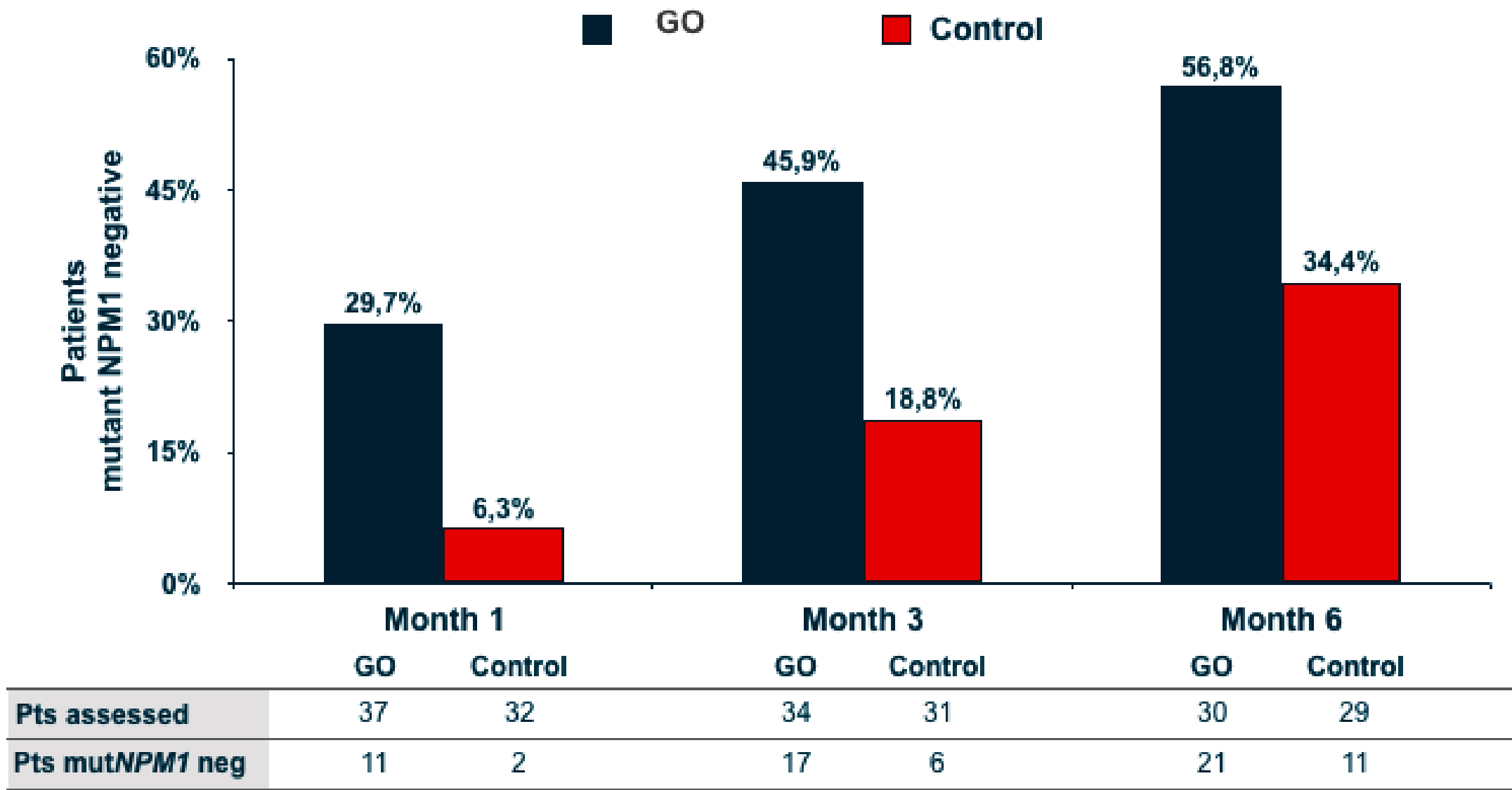
Adapted from Lambert *et al.* 2014

*Percentages calculated from the total number of *NPM1*mt patients in CR who were tested for MRD

CR, complete remission; GO, gemtuzumab ozogamicin; MRD, minimal residual disease; MRD-, minimal residual disease negative; mt, mutation

Lambert J *et al. Oncotarget* 2014;5:6280–6288

Higher MRD-negativity* rates in patients experiencing CR/CRp following GO (*NPM1*)



*MRD negative <0.1% NPM1mut copy number/ABL copy number × 100 (%);
ABL, Abelson murine leukaemia viral oncogene homolog; CR, complete remission; CRp, complete remission with partial haematological recovery of peripheral blood counts;
MRD, minimal residual disease; mutNPM1, mutant Nucleophosmin 1; NPM1, Nucleophosmin 1; pts, patients
Lambert J et al, Haematologica 2018

GIMEMA AML1819 TRIAL: Gemtuzumab ozogamicin plus intensive chemotherapy impacts on the level of post-consolidation measurable residual disease (MRD) in AML

Study Design (AML1819)

• Multicenter, GIMEMA-sponsored clinical trial (NCT04168502)

Patient population:

- Age $\leq$ 60 years
- ELN 2017 **favorable- or intermediate-risk AML**
- FLT3-mutated AML excluded

Treatment backbone:

- Intensive induction and consolidation chemotherapy
 - **Addition of gemtuzumab ozogamicin (GO)**
-

Study Objectives

Primary objectives of AML1819 →

- Determine the rate of **MRD negativity following GO-based induction and consolidation**
- Evaluate the role of post-transplant maintenance

Patient Disposition

- 171 patients enrolled
- 145 patients evaluable for response
- Median age: 53 years (52% male / 48% female)
- Risk category distribution: 52% Favorable Risk (FR); 48% Intermediate Risk (IR)

Clinical Response

- CR/CRi rate: 74% overall
- By ELN risk category: FR: 83%IR: 64%
- 96 patients evaluable for post-consolidation MRD

Post-Consolidation MRD Status

Overall MRD status:

- MRD-negative: 74%
- MRD-positive: 26%

Data indicate a high rate of molecular clearance following GO-based therapy

MRD by Risk Category

- Favorable Risk AML: MRD-negative: 81%
MRD-positive: 19%
- Intermediate Risk AML: MRD-negative: 63%
MRD-positive: 37%

- **AML1819 supports the feasibility of an MRD-oriented treatment algorithm**
- **GO-based regimens achieved high post-consolidation MRD negativity rate**
- **Ongoing follow-up will clarify the impact on long-term clinical outcomes**

ALFA-0701: Summary of all-causality treatment-emergent SAEs*

Preferred terms†	MYLOTARG + chemotherapy (n=131), n (%)	Chemotherapy (n=137), n (%)
Any SAE	88 (67.2)	76 (55.5)
Thrombocytopenia	34 (26.0)	6 (4.4)
Bronchopulmonary aspergillosis	14 (10.7)	10 (7.3)
Septic shock	12 (9.2)	9 (6.6)
Febrile bone marrow aplasia	12 (9.2)	8 (5.8)
Bacterial sepsis	7 (5.3)	0
Acute kidney injury	6 (4.6)	4 (2.9)
Pneumonia	5 (3.8)	6 (4.4)
Sepsis	5 (3.8)	4 (2.9)
Acute respiratory distress syndrome	5 (3.8)	3 (2.2)
Escherichia sepsis	5 (3.8)	1 (0.7)
Veno-occlusive liver disease	5 (3.8)	0
AML	5 (3.8)	0
Hepatocellular injury	4 (3.1)	2 (1.5)
Cholestatic liver injury	3 (2.3)	2 (1.5)
Febrile neutropenia	3 (2.3)	1 (0.7)
Mucosal inflammation	3 (2.3)	1 (0.7)
Disease progression	3 (2.3)	0
Enterococcal sepsis	3 (2.3)	0
Staphylococcal sepsis	2 (1.5)	5 (3.6)
Toxic skin eruption	1 (0.8)	3 (2.2)

Adapted from Lambert et al. 2019. (Suppl.)

*Occurring in $\geq 2\%$ of patients (as-treated population). Defined as all patients who received ≥ 1 dose of study medication and reported according to whether or not MYLOTARG was received; †MedDRA v18.0 applied

AML, acute myeloid leukaemia; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event

Lambert J et al. Haematologica 2019;104:113–119. (Suppl.)

ALFA-0701: Persistent thrombocytopenia and platelet recovery

- Severe persistent thrombocytopenia was defined as platelet count $<50,000/\text{mm}^3$ at 45 days (after Day 1 of the respective treatment phase) in patients experiencing CRp
 - 20 patients discontinued GO as a result of persistent thrombocytopenia*

Laboratory abnormality	GO arm	Control arm
Severe persistent thrombocytopenia		
Evaluable patients	108	101
Patients with persistent thrombocytopenia, n (%)	22 (20.4)	2 (2.0)
Median time to platelet recovery to $50,000/\mu\text{l}$		
During induction, days	34	29
During consolidation 1, days	32	27
During consolidation 2, days	36.5	30

Adapted from Lambert et al. 2019

*As per protocol, patients with platelets $<100,000/\text{mm}^3$ 14 days after the planned start date of their next treatment course were required to discontinue GO
CRp, complete remission with incomplete platelet recovery; GO, gemtuzumab ozogamicin

Lambert J et al. Haematologica 2019;104:113–119

Persistent thrombocytopenia was the most common reason for study drug discontinuation in the GO arm

Preferred term occurring in more than two patients	GO Arm N=131 n (%)	Control Arm N=137 n (%)
Permanent drug discontinuation* in patients with TEAEs	41 (31.3)	10 (7.3)
Thrombocytopenia†	20 (15.3)	0
Veno-occlusive liver disease	4 (3.1)	0
Septic shock	3 (2.3)	2 (1.5)

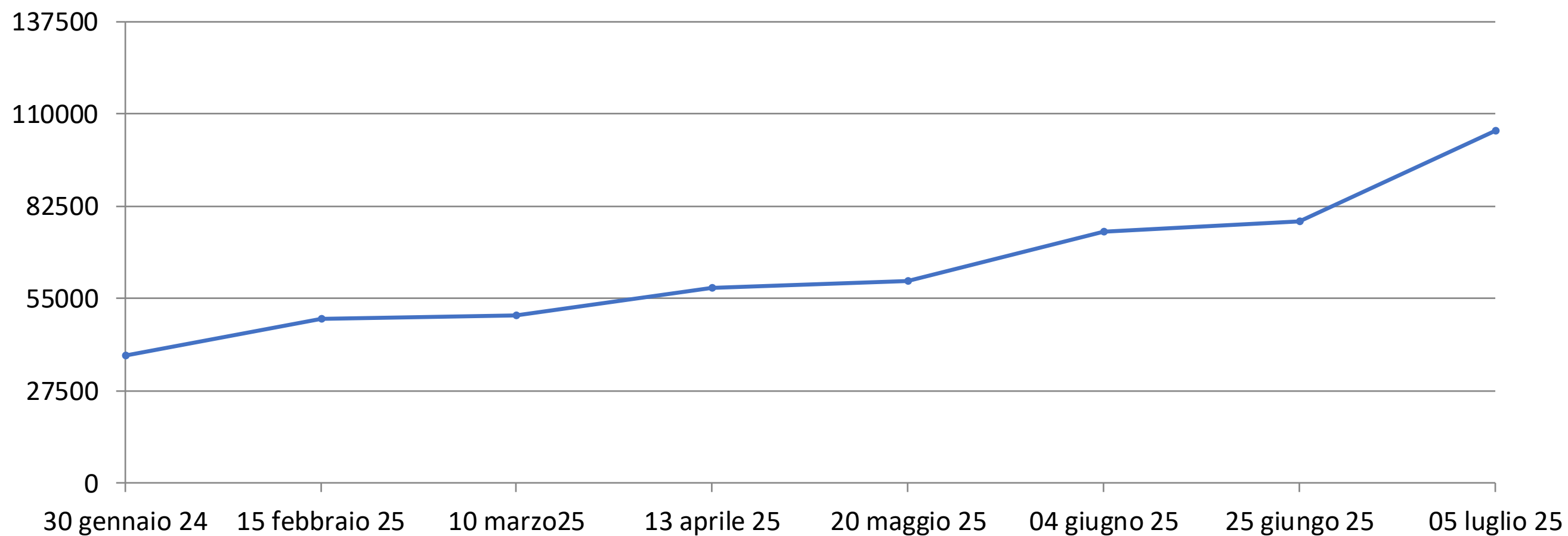
Further investigation of the 20 patients who discontinued due to persistent thrombocytopenia showed no association with severe bleeding.

*Permanent discontinuation of GO or chemotherapy or both

†ALFA-0701 protocol was amended to withhold MYLOTARG to patients during consolidation for persistent thrombocytopenia (<100,000/mm³) not recovered on Day 14 after the scheduled date of consolidation therapy

Lambert J et al, Haematologica 2018

Andamento della conta piastrina dal termine del II consolidamento



ALFA - 0701:Time to Platelet Recovery and Persistent Thrombocytopenia

	GO + DNR/Ara-C			DNR/Ara-C		
Patients with persistent thrombocytopenia [†]						
Overall, n±/N (%) [§]	22/108 (20.4)			2/101 (2.0)		
	Induction n=108	Conso. 1 n=94	Conso. 2 n=76	Induction n=101	Conso. 1 n=94	Conso. 2 n=85
By treatment phase, n (%)	8 (7.4)	8 (8.5)	10 (13.2)	1 (1.0)	0 (0.0)	2 (2.4)
Time to platelet recovery						
	Induction n=131	Conso. 1 n=97	Conso. 2 n=82	Induction n=137	Conso. 1 n=97	Conso. 2 n=89
Patients recovered to 50,000/mm ³ , n [±] (%)	109 (83.2)	92 (94.8)	80 (97.6)	118 (86.1)	86 (88.7)	85 (95.5)
Median time to recovery, [¶] days	34.0	32.0	36.5	29.0	27.0	30.0
Patients recovered to 100,000mm ³ , n [±] (%)	99 (75.6)	71 (73.2)	70 (85.4)	111 (81.0)	80 (82.5)	82 (92.1)
Median time to recovery, [¶] days	35.0	35.0	43.0	30.0	28.0	32.0

*Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received; [†]Persistent thrombocytopenia was defined as platelet count not recovered to 50,000/mm³ at 45 days after day 1 of the respective treatment phase in patients experiencing CRp; [‡]n: number of patients with events; [§]Overall number of patients with persistent thrombocytopenia after any phase; ^{||} N: number of patients evaluable for thrombocytopenia was used as the denominator for calculating the percentage of patients with persistent thrombocytopenia. Patients evaluable for thrombocytopenia were those who received each of the courses and had platelet laboratory results collected during the retrospective data collection; [¶]Based on Kaplan-Meier estimate

Ara-C = cytarabine; DNR = daunorubicin; Conso = Consolidation; CRp = complete remission with incomplete platelet recovery; GO = gemtuzumab ozogamicin

Etiopathogenesis of prolonged thrombocytopenia during GO therapy

Gemtuzumab Ozogamicin Treatment Results in Decreased Proliferation and Differentiation of Human Megakaryocytes but Does Not Inhibit Mature Platelet Function

Allison Vitsky¹, Aida Sacaan¹, Wenyue Hu¹, Martin Finkelstein¹,
and William Reagan²

Impact on Megakaryocytes

GO decreases proliferation and differentiation of human megakaryocytes, affecting platelet production.

Platelet Function Preservation

Despite megakaryocyte effects, GO does not impair mature platelet aggregation or function under tested conditions.

Immune-Mediated Mechanisms

Prolonged thrombocytopenia may involve immune processes such as antibody-mediated platelet clearance.

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Platelet Function Assessment

In vitro assays show no significant impairment of platelet aggregation by GO, despite challenges in testing impaired patient populations.

GO Effect on Healthy Platelets

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GO at clinical concentrations did not affect platelet aggregation in healthy donor samples measured by light transmittance aggregometry.

GO and Anticoagulant Interaction

GO did not exacerbate the effects of common anticoagulants on platelet aggregation in healthy platelet samples.

GO in Uremic Plasma

GO showed no significant impact on platelet aggregation in plasma from uremic patients, except isolated cases linked to other medications.

Management and Monitoring of thrombocytopenia in GO-treated patients

- Monitor complete blood counts prior to each dose
- Perform routine clinical and laboratory surveillance during and after treatment
- Monitor for signs and symptoms of:
 - Infection or bleeding/hemorrhage
 - other manifestations of myelosuppression

In cases of severe bleeding, hemorrhage, or persistent thrombocytopenia:

- consider dose delay or permanent discontinuation of GO
- provide supportive care according to standard clinical practice
 - If platelet count recovers to $\geq 100,000/\text{mm}^3$ within 14 days following the planned start date of the consolidation course: initiate treatment with GO
 - If platelet recovery: takes longer than 14 days to reach $\geq 50,000/\text{mm}^3$, or does not recover to $\geq 50,000/\text{mm}^3 \rightarrow$ re-evaluate consolidation therapy and perform a bone marrow aspirate to reassess patient status

Treatment Adjustments

Dose delays or stopping GO therapy, along with supportive care, are advised for severe bleeding or persistent thrombocytopenia.

Permanent discontinuation

Clinical trial protocols recommend avoiding GO during consolidation phase in patients experiencing severe adverse events during induction.

Conclusioni

- L'aggiunta di GO alla chemioterapia intensiva è efficace in LAM CD33+ a rischio favorevole
- GO+CHT intensiva è associato ad un elevato tasso di MRD negatività (soprattutto in NPM1 mut.)
- Tossicità ematologiche ed extraematologiche sono gestibili con monitoraggio laboratoristico per identificare precocemente eventuali tossicità
- L'outcome post-trapiantologico non è gravato da maggiore tossicità nei pazienti trattati con GO (no maggiore VOD, simile NRM)

Grazie per
l'attenzione